DOI:
10.1016/j.ajodo.2017.10.021

Document Version
Peer reviewed version

The effect of supplemental vibrational force on space closure, treatment duration, and occlusal outcome: a multicenter randomized clinical trial

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ABSTRACT

Introduction: A multicenter parallel three-arm randomized clinical trial was carried out in three UK university hospitals to investigate the effect of supplemental vibratory force on space closure and treatment outcome with fixed appliances. **Methods:** Eighty-one subjects <20 years of age with mandibular incisor irregularity undergoing extraction-based fixed-appliance treatment were randomly allocated to supplementary (20-minutes/day) use of an intra-oral vibrational device (AcceleDent®) (Accel-group) (n=29), an identical non-functional (sham) device (Accel-sham) (n=25), or fixed-appliances only (Fixed-only) (n=27). Overall space closure in the mandibular arch was measured from dental study casts taken at start of space closure (T1), at the following appointment (T2), and at completion (T3). Final records were taken at completion of treatment (T4). Data were analyzed blindly on a per-protocol basis with descriptive statistics, one-way analysis of variance, and linear regression modeling with 95% Confidence Intervals (CI). **Results:** Sixty-one subjects remained in the trial at start of space closure with all three groups comparable for baseline characteristics. The overall median rate of initial mandibular arch space closure (primary outcome) was 0.89 mm/month with no difference for either the Accel-group (difference=-0.09 mm/month; 95% CI=-0.39 to 0.22 mm/month; P=0.57) or Sham-group (difference=-0.02 mm/month; 95% CI=-0.32 to 0.29 mm/month; P=0.91) compared to the Fixed-only group. Similarly, no significant differences were identified between groups for secondary outcomes, including overall treatment duration (median=18.6 months; P>0.05), number of visits (median=12; P>0.05) and % improvement in Peer Assessment Index (median=90.0%; P>0.05). **Conclusions:** Supplemental vibratory force during orthodontic treatment with fixed appliances does not affect space closure, treatment duration, total number of visits or final occlusal outcome. **Registration**: NCT02314975. **Protocol**: The protocol was not published before trial commencement. **Funding**: AcceleDent® units were donated by the OrthoAccel Technologies Inc, Texas USA; no contribution into the conduct or writing of this study was made by the manufacturer.

INTRODUCTION

Despite numerous innovations and advances in orthodontic appliance design and application, the average duration of comprehensive treatment with fixed appliances has remained relatively stable at just under twenty months [1]. Accelerated orthodontic treatment is desirable; not only to limit the social and dental inconvenience of wearing fixed appliances, but also to help reduce the established risks of iatrogenic damage [2]. Over the years, numerous innovations and adjuncts have been described that purport to speed up tooth movement and reduce overall treatment time. There is currently no robust evidence for faster tooth movement and reduced treatment time in association with any particular appliance design [3,4], bracket prescription [5], archwire composition [6] or treatment adjunct [7]. The sole exception are surgical interventions, such as corticotomies or piezocision that do seem to accelerate tooth movement, albeit on a relatively short-term basis [8]. However, most of these surgical techniques are invasive and may not be readily acceptable to the majority of subjects [9]. Therefore, continued efforts are directed towards the search for a safe, predictable and acceptable method to reduce orthodontic treatment time, without compromising clinical results.

The use of supplemental vibrational force has been advocated as a method of speeding up orthodontic tooth movement. This involves the application of low-level vibration directly to the dentition as it is subjected to orthodontic force. The basic principle underlying orthodontic tooth movement is the ability of alveolar bone to respond with remodeling following the application of external force [10]. Using this principle, vibrational force has been shown to aid in the maintenance of bone mass in post-menopausal women [11] or subjects with reduced mobility and prolonged bed-rest [12-14]. At the same time, data from animal models indicates an increased rate of tooth movement, osteoclastic activity and bone remodeling within the periodontium [15,16]. These data have been used to inform the development of commercial vibrational appliances for clinical use, one of which is AcceleDent® (OrthoAccel Technologies, Houston, Texas USA). This is a hands-free portable device consisting of an activator unit and removable thermoplastic occlusal wafer, which the patient bites onto. The activator unit vibrates and delivers a force of 0.2 N at a frequency

of 30 Hz to the dentition. The manufacturer suggests that it is used for 20 minutes per day in order to increase the speed of tooth movement and thereby reduce treatment time.

Clinical benefits from the use of supplemental vibration have been reported from case reports and non-randomized retrospective cohort studies [17-20]. These investigations have shown increases in the rate of orthodontic tooth movement and a reduction in treatment time, but their non-randomized and retrospective design exposes them to potential bias and exaggerated treatment effects [21]. There is data from randomized studies demonstrating statistically significant effects of supplemental vibration when delivered using either AcceleDent or a vibrating toothbrush during orthodontic treatment [22,23]. These data are at both the clinical and biochemical level; but again, the methodological design of both these studies predisposes them to a high risk of bias [24]. These encouraging results have not been confirmed by other randomized clinical trials investigating rates of tooth movement, which have found no significant benefit from supplemental vibrational force [25-27]. However, these trials have only reported on the initial alignment phase with fixed appliances and no robust evidence exists to date in relation to rates of space closure or overall treatment time when using fixed appliances with supplemental vibration.

Specific objectives and hypothesis

The aim of this study was to investigate the effect of AcceleDent appliance usage on the outcome of fixed appliance orthodontic treatment. The primary outcome measure for this component of the trial was initial rate of mandibular arch space closure, whilst secondary outcomes included overall rate of mandibular space closure, treatment duration, number of visits, appliance breakages and PAR reduction during treatment. The null hypothesis is that the use of supplemental vibrational force does not improve the rate of mandibular arch space closure, overall treatment duration or outcome in subjects undergoing comprehensive extraction treatment using fixed appliances.

MATERIALS AND METHODS

Trial design and any changes after trial commencement

Data for this investigation were gathered from the follow-up of a three-arm parallel randomized controlled trial comparing the effect of supplemental vibrational force on orthodontic tooth alignment [27] and are reported according to the CONSORT statement [28]. Ethical approval was obtained from the UK National Research Ethics Service (South East London REC 3: 11/LO/0056) and written-informed consent received from all parents, guardians and subjects. This trial was registered at the European Clinical Trials Database (EudraCT, 2014-004211-37) on September 29, 2014 and ClinicalTrials.gov (NCT02314975) on November 25, 2014. No changes to methodology occurred after trial commencement. There were no changes to the trial after commencement.

Participants, eligibility criteria and settings

Participants were recruited from subjects referred to the orthodontic departments at King's College London Dental Institute (Guy's Hospital); the Royal Alexander Children's Hospital, Brighton, Sussex; and William Harvey Hospital, Ashford, Kent, United Kingdom. The former is based in a dental school and the latter two are based in regional hospitals. All offer comprehensive orthodontic treatment for children and adults. Eligibility criteria have been previously described [27] and included: (1) <20 years-old at start of treatment; (2) medically fit and well; (3) in the permanent dentition; (4) presence of mandibular incisor irregularity; and (5) bilateral mandibular first premolar extraction as part of the treatment plan.

Interventions

Participants were randomly assigned to one of three groups: (1) Pre-adjusted edgewise fixed-appliance treatment with daily-use of an AcceleDent® (OrthoAccel® Technologies, Texas, USA) vibrational device (Accel-group); (2) Pre-adjusted edgewise fixed-appliance treatment with daily-use of a non-functional (sham) AcceleDent device (Accel-sham) provided by the manufacturer; and (3) Pre-adjusted edgewise fixed-appliance treatment alone (Fixed-only). Subjects allocated to adjunctive devices were given direct verbal and written instruction on operation and usage,

instructed to use it for 20 minutes/day at a time of their choosing and informed that a timer was part of the device, which allowed the investigator to monitor compliance [27].

Bonding method and fixed appliances were standardized (pre-coated 3M Victory-series brackets; MBT prescription; bonding of lower second permanent molars) with a pre-determined sequence of 0.014-inch, 0.018-inch, 0.017 x 0.025-inch nickel titanium (Ni-Ti) and 0.019 x 0.025-inch stainless steel (SS) archwires. Data collection relating to the alignment phase of treatment took place at start of treatment (baseline), placement of 0.018-inch Ni-Ti (initial alignment) and 0.019 x 0.025-inch SS (completion of alignment) and have been previously reported [27,29,30]. All appointments were made as part of the routine orthodontic treatment provided within the participating departments and scheduled at approximately 6-week intervals. No bite-planes, auxiliary-arches, or headgears were used during the period of space closure, but inter-maxillary elastics were permitted as prescribed. All subjects were treated by senior orthodontists (ATD, NJ, CS, JG, MTC) or postgraduate specialist trainees (NRW, MA) under their direct supervision.

For this component of the trial, space closure was initiated at the first visit following placement of a 19 x 25-inch SS working archwire (completion of alignment) and undertaken using 9 mm Ni-Ti coil springs attached from the first molar to hooks placed on the archwire between lateral incisor and canine, and stretched to no more than twice their length, as per manufacturer instructions. Data was collected at the start of mandibular space closure (T1); at the first visit following initiation of space closure (T2), at the end of space closure in the mandibular arch (T3) and at completion of treatment on removal of the fixed appliances (T4). Coil springs were checked during routine adjustments between T1-T3 and retied. If there was any sign of damage they were replaced with a spring of the same dimensions. Specifically, dated mandibular (T1-T3) and both maxillary and mandibular (T4) alginate impressions were taken for the generation of dental study casts.

For mandibular arch space closure: space was measured using Mitutoyo IP67 150-mm digital-calipers (Mitutoyo, UK) by placing the caliper tip from (the most concave) contact point-to-contact point between mandibular second premolar and canine bilaterally and calculating a mean

value for each subject. A sample of 20 subjects was randomly chosen and re-measured by the same assessor (MA) after two weeks for repeatability. Repeatability and agreement of the measurements were assessed with the Concordance Correlation Coefficient [31] and the Bland-Altman method [32]. Monthly rates of mandibular arch space closure were calculated by dividing mean space closure value by the exact number of space closure days divided by 30 (days).

All subjects in the trial had first premolar extractions in the mandibular arch. In the maxillary arch, all subjects had a single tooth extracted in each quadrant but these extraction patterns varied and were classified as those with premolar extractions, canine or incisor extractions or a combination.

For Peer Assessment Rating (PAR) index [33]: dental casts taken at baseline and T4 were scored by a single calibrated examiner.

Outcomes (primary and secondary)

The primary outcome measure for this component of the trial was initial rate of mandibular arch space closure (T1-T2, calculated as mm/month). Secondary outcomes included overall rate of mandibular arch space closure (in mm/month), overall treatment duration (in months), overall number of visits, number of appliance breakages and both absolute and relative (%) PAR reduction during treatment.

Sample size calculation

The primary outcome for the present component of the trial was initial rate of mandibular arch space closure. No formal sample size calculation was performed for this component because it is a follow-up examination of a previous randomized clinical trial [27]. However, a previous randomized trial investigating three methods of orthodontic space closure calculated that 11 subjects per group (33 subjects in total) would yield a power of 90% to detect a clinically significant difference in space closure at quadrant level (0.75 ± 0.50 mm/month) with α=5% [34], which indicated that the primary outcome for this component of the trial was adequately powered.

Randomization

The randomization sequence was computer-generated using GraphPad online software (http://www.graphpad.com/quickcalcs/index.cfm) with participant allocation undertaken centrally at King's College London, independently from the clinical operators following recruitment (allocation concealment) [35 35]. No restricted randomization or stratification was utilized.

Blinding

By the nature of the trial intervention, subjects and treating clinicians were aware of treatment group allocation. Dental casts were coded so that all measurements were undertaken blind. All dental cast linear measurements were carried out blind by a single investigator (MA). PAR scoring was also conducted blind for all dental casts by a single calibrated examiner (YK).

Statistical analysis

Statistical analysis was conducted on a per-protocol basis and blinded with a coded dataset, where the code was broken after final provision of the analysis results. Data normality was checked via visual inspection of distributional diagrams and formal testing with the Shapiro-Wilk test. As all outcomes were non-normally distributed ($P<0.05$), descriptive statistics consisted of medians and inter-quartile ranges (IQRs). Initial crude differences among randomized groups were calculated with Kruskal–Wallis one-way analysis of variance.

Subsequent linear regression models were fitted with independent variables for either the randomization group (crude analysis) or additional confounders, including the possible influence of study center [36]. Choice of the latter was based on both on clinical judgment and on whether bivariable model fit improved with a criterion-based method using a model with just the dependent variable [37]. Assumptions of linear regression for all fitted models were checked including graphical and statistical tests for homoscedasticity of residuals, multicollinearity of predictors, and model

misspecification. Results are reported as unstandardized coefficients and 95% confidence intervals (CIs) with α set at 5%.

Post hoc explorative analyses were conducted to investigate any systematic differences across centers in terms of average time interval between appointments. Additionally, interactions of randomized interventions' effects with baseline severity of irregularity, baseline extraction spaces and baseline PAR scores were investigated (with cut-offs of 7 mm, 7 mm and 30 points, respectively). The main (per-protocol) analysis that was conducted excluded (i) subjects that reported not using their Accel or Accel-sham appliance (n=9), (ii) cases of early fixed appliance removal at subject request (n=2), cases with more than 3 missed appointments (n=5), those with more than 5 episodes of fixed appliance breakage (n=2), one case with an impacted maxillary canine and one case undergoing orthognathic surgery. A separate sensitivity analysis was performed with the intention-to-treat sample by including all excluded subjects with available data and compared to the main analysis for robustness.

RESULTS

A CONSORT diagram demonstrating subject flow through the trial is shown in Figure 1. Eighty-one subjects were recruited into the trial between July 2011-May 2014, with 29 allocated to the Accel-group, 25 to Accel-sham and 27 to Fixed-only. The total randomized sample consisted of 40 males and 41 females with a mean age of 14.1 (SD, 1.7) years. The mean age of subjects allocated to the Accel-group was 13.9 (SD 1.6) years, to Accel-sham 14.1 (SD 1.9) years and to Fixed-only was 14.4 (SD 1.8) years.

Table 1 shows baseline demographics of subjects investigated in the present component of the trial. A total of 61 subjects remained in the trial at T1, which included 22 in the Accel-group, 19 in the Accel-sham, and 20 in the Fixed-only group. These three groups were comparable for all patient characteristics at baseline (Table 1).

Outcomes and estimation

The mean time period from T1-T2 was 68 ±28 days and from T1-T3 was 172 ±79 days. For the primary outcome of initial rate of mandibular arch space closure the median across all randomized subjects was 0.89 mm/month (IQR=0.56 to 1.33 mm/month) with no significant differences among groups (P=0.61; Figure 2; Table 2). In addition, no significant differences among groups were identified for any secondary outcomes, including overall rate of mandibular arch space closure (median [IQR]=0.74 [0.56 to 1.00] mm/month), overall treatment duration (median [IQR]=18.57 [16.3 to 23.9] months), number of visits (median [IQR]= 12 [10 to 16] visits), number of breakages (median [IQR]=2 [1 to 3] breakages), final PAR score (median [IQR]=3 [2 to 4] points) and absolute (median [IQR]=28 [21 to 35] points) or % improvement in PAR score (median [IQR]=90.0% [84.6% to 93.8%]) (P>0.05 in all instances).

These findings were also confirmed by regression analyses with either crude (including only experimental groups and study center-effects) or adjusted (experimental groups, study center-effects, and confounders) models (Table 3). No differences could be found in initial space closure rate between either the Accel-group or Accel-sham and the Fixed-only group (P=0.57 and P=0.91, respectively). The only factors that significantly influenced space closure rate were patient gender, extraction category in the maxillary arch and the amount of initial space to be closed (with male patients, extraction of upper anterior teeth, and increased baseline space positively associated with closure rate; P<0.05 in all three cases; Table 3).

No differences in the average time interval between appointments could be found among the three study centres (Supplementary Table 1).

No significant interactions of treatment effects could be found with baseline severity of irregularity, extraction spaces to be closed or PAR score (Supplementary Table 2), indicating that the effect of an Acceledent appliance did not differ between ‘easy’ and ‘difficult’ cases.

Repeated measurements, sensitivity analysis, and harms

The agreement of repeated measurements was found to be excellent by the Bland-Altman limits of agreement (mean difference <0.05 mm) and the CCC (CCC>0.99; Supplementary Table 3).

Finally, the intention-to-treat results of the sensitivity analysis (Supplementary Table 4-8) contributed to the robustness of the analysis, as they were in complete agreement with the per-protocol analysis (Tables 1-3).

The only harms assessed in this trial were appliance breakages, where there were no significant differences among randomized groups (Tables 2-3).

DISCUSSION

Main findings in the context of existing evidence

The results of this study show no clinical or statistical difference between groups in relation to the initial rate of mandibular arch space closure. There was likewise, no significant difference among groups for overall space closure rate in the mandible, total treatment time, number of visits, breakages or final static occlusal outcome (measured with PAR), indicating that the use of supplemental vibrational force had no beneficial effect on orthodontic treatment with fixed appliances. There was actually an association between use of AcceleDent and increased overall treatment time but this was only close to significance (P=0.07; Table 2). It is difficult to explain why this association might have existed, given the equivalence between randomized groups demonstrated in all the other outcomes investigated, but it does support previous research showing that the use of vibrational force does not influence rate of tooth movement during alignment with fixed appliances [25-27]. However, it is at odds with other studies that have shown increased rates of maxillary canine retraction and molar distalization in the presence of vibration [18,22,23] and indeed, reductions in time to achieve perceived levelling [17] and completion of treatment in highly selected cases [20].

In the present investigation, both rates of space closure in all three groups were comparable to other studies using Ni-Ti coil springs. Previous research investigating space closure using sliding mechanics have reported rates per month ranging from 0.64 mm to 2.04 mm [34,38-43]. The median in this study across all three groups was 0.89 mm per month, with no significant difference among groups. Additionally, there was a significant relationship between the amount of

extraction space at the start of the study and both space closure rates: the larger the total extraction space the higher the rate of space closure. This may be due to a greater activation of the Ni-Ti springs over larger extraction spaces or a statistical artifact. The initial rates of space closure were higher than the overall rates reported for all three groups. This may be a reflection of the time-intervals between appointments; the subjects were seen approximately every six to eight weeks as per standard clinical practice (averaged time-interval between appointments: median=50.7 days; P>0.05 across centers; Supplemental Table 1). Therefore, extraction spaces might well have been fully closed in certain cases some time before the T3 records were actually collected, resulting in a reduction of the extrapolated measured overall rate of space closure.

While all participants had lower first premolars extracted, extraction patterns in the maxillary arch varied according to malocclusion and the specific treatment plan. While this did not directly impact upon treatment duration, number of visits or the overall rate of space closure, it did affect the initial rate in the lower arch. However, no post hoc pairwise comparisons were performed, as this was not the main scope of the trial, patient distribution was fairly uneven and to avoid unnecessary Type I error inflation. Similarly, the prescription and use of inter-arch elastics was not formally measured as part of the trial and this could potentially have influenced space closure rates. However, the distribution of class II and III malocclusions was comparable between intervention groups (Table 1) and unlikely to have been a significant cofactor during space closure.

Whilst some anecdotal evidence exists on the matter, to the authors' knowledge no study has reported on the effect of supplemental vibratory force on overall duration or outcome of comprehensive fixed-appliance treatment [19,20,44]. The results of this trial cannot support a reduction in treatment time, fewer visits, or a greater PAR reduction in subjects who used the AcceleDent device. The treatment duration reported in this study is comparable to that reported in previous prospective studies for extraction-based treatment with fixed appliances [1] and to the average treatment time reported in a recent systematic review [29].

The mean PAR reduction in this trial for all three groups was above 22 points (or 70% of the baseline PAR) indicating a great improvement in relation to occlusal outcomes, irrespective of

the use of either the active or sham Acceledent device [33]. This is in part a reflection of the inclusion criteria, particularly in relation to the severity of crowding or malalignment. Unsurprisingly, the greater the initial PAR score (and therefore, the more severe the case), the greater the relative improvement in the PAR score with treatment. The reduction in PAR reported in this study showed the cases were treated to a high standard in all three groups, implying no operator bias or indication that the study subjects' treatment was rushed in an attempt to produce positive findings for the trial intervention.

Limitations

Like many long-term clinical trials that follow subjects to the end of treatment, this study was subject to significant drop-out, making it potentially susceptible to attrition bias, particularly in relation to long-term non-compliance with the AcceleDent appliance. However, drop-out was similar across the three groups (24% overall; 24%, 24% and 26% per group; Figure 1), which in combination with the comparability of the finally-analyzed sample for age, initial irregularity and presenting malocclusion, implies that any effect on trial outcomes might be negligible. In addition, even with the relatively high levels of drop out, the numbers in each group were still greater than those required from the sample size calculation for primary outcome [34], making the analyses and findings valid and applicable. However, the analysis for some secondary outcomes might be underpowered and caution is warranted in their interpretation.

It is also not possible to state that the applied space-closing mechanics were absolutely consistent between extraction sites throughout the sample because the forces were not quantified and there is evidence that force magnitude can influence rate of tooth movement [45,46]. Some individual variation will exist amongst clinicians and whilst the activation scheme was standardized a priori so that the springs were not stretched more than twice their length, variance can exist between forces delivered by different springs activated to the same distance [47-50]. The age of eligibility for the study was <20 years, which means that some variation in development and relative maturity may have existed between groups, which can also affect rate of tooth movement

[45]. This could also partially explain the gender effects reported, in that for the same chronological age, female subjects could be more mature and less biologically responsive to the same orthodontic force than their male counterparts.

The subjects in this investigation were all undergoing routine orthodontic treatment in three clinical settings. Appointments were made at approximately six to eight week intervals but it is possible that some data collection took place beyond the specific time-point of achieving the desired tooth movement, specifically the completion of space closure and completion of overall treatment. Unless subjects are seen almost weekly this is a potential confounder, but difficult to avoid when conducting clinical studies in a real-world setting. The manufacturer of this appliance does not mention that treatment modalities need to be changed or that patients need to be seen more regularly when using this device. We have tested the use of supplemental vibration with fixed appliances on adolescent patients using conventional treatment mechanics. For the claims that have been made in relation to the use of vibrational force to be of relevance to practicing clinicians they need to be testable in such an environment and clinically relevant.

While the operators and analyst in this study were blinded to initial allocation, the subjects were asked to use the AcceleDent appliance immediately before each clinical appointment, which made it impossible to blind the operator to group allocation. Asking subjects to bring their device and use it prior to each appointment was done as a means of allowing the operator to verify continued appliance usage and compliance. However, we acknowledge that operator-blinding would have been a desirable methodological addition. Although true blinding of participants has been claimed in a previous randomized investigation of AcceleDent, it is difficult to believe that most subjects appropriately informed about the nature of such a trial during the consent process, would not realize fairly soon that they had been allocated a non-functional (non-vibrating) device [23]. All the AcceleDent units (both active and sham) in the present study contained electronic timers that could be read off an LED screen in the housing unit; however, these were the first timers to be incorporated in this device by the manufacturer and unfortunately, they did not work. The collection of formal compliance data was therefore not possible and the effect of inadequate

compliance on the results of this trial cannot be completely ruled out. The use of self-monitoring and reporting was considered during the planning of this trial, but this can result in over-estimation of compliance [51]. Advocates of vibrational force have been quick to criticize the methodology associated with prospective RCTs investigating this treatment intervention [52]. No clinical trial is perfect, but these criticisms should be considered in the knowledge that the fundamental methodology associated with retrospective studies that have found differences is highly likely to be associated with bias [17,18,20]. It is well established in medical research that retrospective study designs produce over-estimation of treatment effects and this includes clinical orthodontics [21]. The accurate measurement of compliance is clearly an important issue and in the present study, despite repeated monitoring during the trial and the exclusion of non-compliers from the per-protocol analysis, definitive data is lacking. However, the only available compliance data for these devices relates to either patient logbooks or evidence of the device being switched on, not switched on and necessarily in the mouth. We acknowledge this, but it is important to emphasize that compliance data is relevant for all studies, irrespective of whether they find positive or negative results. Two of the most commonly cited investigations endorsing the use of vibrational force to accelerate tooth movement (methodological flaws aside) report no formal compliance data [17,23].

Generalizability

The study was carried out in three hospital orthodontic departments that offer comprehensive treatment for adolescents. The treatment was carried out either by experienced clinicians or by postgraduates under the direct supervision of experienced clinicians. The range, type and severity of malocclusions treated in this study in adolescent subjects using a common fixed-appliance system typical of most orthodontic caseloads**.** Also, the potential issues of compliance documented again are problems encountered in everyday clinical practice. We therefore feel that the results are applicable to orthodontic clinical practice for adolescent subjects treated with extractions in the majority of clinical settings.

CONCLUSIONS

This multicenter randomized controlled trial has investigated the influence of supplemental vibrational force on orthodontic tooth movement. In this component of the trial we report no benefits of vibration in terms of mandibular space closure rate, treatment duration and final treatment outcome. Within the limitations of this study and based upon cumulative prospective evidence we conclude that whilst the use of supplemental vibrational force with fixed appliances is not associated with increased appliance breakage it does not provide any advantages. Practitioners should consider this when recommending supplemental vibrational force to their subjects on the basis of reducing treatment time or any other added benefits. From the apparent results of this study, patients who purchase these vibration devices have the burden of costs without the advertised benefits.

Acknowledgements

We are grateful to OrthoAccel Technologies, who graciously agreed to participate in this prospective randomized investigation and provide both functional and sham AcceleDent units to us at no cost. This investigation was undertaken independently from OrthoAccel Technologies Inc. The authors declare no potential conflicts of interest with respect to the authorship and/or publication of this research article.

Figure Legends

Figure 1 CONSORT diagram showing the flow of subjects through the trial. B=Baseline; T1=Start of space closure; T2=First visit following T1; T3=End of space closure; T4=Completion of treatment. (*) n=1 not analyzed for PAR score because the final model was not available. (+) It should be noted that in the Accel and Accel-sham groups 1 subject was lost from each group because they discontinued using the device; and in the fixed-only group, 1 subject was lost through early removal of the fixed appliance, all were lost prior to the completion of incisor alignment [27]. In total, 6 subjects were lost from Brighton, 8 subjects were lost from Guys and 6 subjects were lost from Canterbury.

Figure 2 Cumulative graph showing predicted marginal treatment effects for primary and secondary outcomes of the present trial. Results are plotted as unstandardized regression coefficients with 95% CIs (blue) based on the adjusted models from Table 3. The graph has been augmented with contours of effect magnitude (grey shades) based on the SD in the reference group (Fixed-only) for each outcome.

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Table 1. Baseline characteristics of trial subjects

Characteristic	Overall	Accel-group	Sham-group	Fixed-only group
Patient number - n	61	22	19	20
Center BRIGHTON - n (%)	27 (44%)	8 (36%)	11 (58%)	8 (40%)
Center GUYS - n (%)	10 (16%)	4 (18%)	1 (5%)	5 (25%)
Center 3 - CANTERBURY (%)	24 (39%)	10 (45%)	7 (37%)	7 (35%)
Male - n (%)	30 (49%)	11 (50%)	8 (42%)	11 (55%)
Age - mean (SD)	13.9 (1.5)	13.6 (1.4)	13.9 (1.5)	14.3 (1.7)
Baseline irregularity - mean (SD)	7.8 (3.2)	7.5 (3.2)	7.9 (3.3)	8.0 (3.3)
Baseline PAR* - mean (SD)	33.0 (11.0)	34.0 (11.7)	30.9 (9.6)	33.9 (11.9)
Class I - n (%)	22 (36%)	8 (36%)	7 (37%)	7 (35%)
Class II - n (%)	22 (36%)	9 (41%)	6 (32%)	7 (35%)
Class III - n (%)	17 (28%)	5 (23%)	6 (32%)	6 (30%)
Premolar extractions - n (%)**	53 (87%)	21 (95%)	17 (89%)	15 (75%)
Canine/incisor extractions - n (%)**	2 (3%)	0 (0%)	0 (0%)	2 (10%)
Mixed extractions - n (%)**	6 (10%)	1 (5%)	2 (11%)	3 (15%)
Extraction spaces - mean (SD)	8.0 (2.3)	8.3 (2.4)	8.2 (2.2)	7.4 (2.4)

SD, standard deviation; PAR, peer assessment rating.
*n=59 not 61 subjects (21, 19, and 19 subjects in groups Accel, Sham, and Fixed-only, respectively)
** All subjects had mandibular arch first premolar extractions; these extraction categories relate to teeth that were extracted in the maxillary arch.

Table 2. Descriptive statistics and crude differences across groups. Data are given as median and interquartile range (IQR) and not as mean and standard deviation, as they are not normally distributed

	Accel-group			Sham-group			Fixed-only group			
	n	median	IQR	n	median	IQR	n	median	IQR	P*
Initial rate of space closure T1-T2 (mm/month)	22	0.82	0.48, 1.33	19	0.89	0.56, 1.13	20	0.95	0.65, 1.47	0.61
Monthly space closure rate T1-T3 (mm/month)	22	0.82	0.62, 1.06	19	0.68	0.57, 0.80	19	0.76	0.52, 1.01	0.42
Treatment duration (months)	22	20.45	17.63, 25.23	19	16.73	15.33, 22.07	20	17.64	14.87, 23.89	0.07
No of visits	22	14.5	11.0, 17.0	19	11.0	10.1, 14.0	20	11.0	9.5, 16.0	0.13
No of breakages	22	2.0	1.0, 3.0	19	2.0	1.0, 3.0	20	2.0	1.0, 2.0	0.95
PAR at T6	21	3.0	2.0, 6.0	19	3.0	2.0, 4.0	19	3.0	2.0, 4.0	0.60
PAR Improvement	21	28.0	21.0, 38.0	19	27.0	20.0, 35.0	19	29.0	24.0, 31.0	0.91
PAR Improvement %	21	88.9	80.9, 94.4	19	90.0	87.5, 92.0	19	91.2	85.0, 93.5	0.74

PAR, peer assessment rating
* from Kruskal-Wallis test

Table 3. Results of the crude and adjusted regression models for primary and secondary outcomes

			Crude model: only group			Adjusted modeling: group and confounding factors		
			b	95% CI	P	b	95% CI	P
Initial rate of space closure (T1-T2)	Group (Ref=Fixed-only)	Accel	-0.10	-0.44,0.25	0.57	-0.07	-0.39,0.25	0.67
		Sham	-0.03	-0.39,0.32	0.85	-0.02	-0.34,0.31	0.92
	Gender		NT			0.29	0.02,0.56	0.04
	Malocclusion		NT			0.12	-0.05,0.28	0.15
	Extraction		NT			0.24	0.02,0.47	0.03
	Spaces T3		NT			0.08	0.03,0.14	0.005
Overall rate of space closure (T1-T3)	Group (Ref=Fixed-only)	Accel	0.11	-0.19,0.40	0.47	0.11	-0.17,0.39	0.43
		Sham	-0.11	-0.41,0.190	0.45	-0.12	-0.41,0.16	0.39
	Gender		NT			0.18	-0.05,0.41	0.12
	Malocclusion		NT			0.15	0.01,0.29	0.04
	Extraction		NT			0.16	-0.03,0.35	0.11
	Spaces T3		NT			0.05	0.00,0.10	0.03
Treatment duration	Group (Ref=Fixed-only)	Accel	3.00	-0.39,6.40	0.08	2.19	-0.70,5.07	0.13
		Sham	-0.27	-3.79,3.26	0.88	0.85	-2.21,3.90	0.58
	Gender		NT			-0.84	-3.24,1.57	0.49
	PAR T1		NT			0.11	-0.01,0.22	0.07
	Center (Ref=Brighton)	Guys	NT			3.21	2.06,9.14	0.002
		Ashford	NT			-4.31	2.84,8.27	<0.001
Number of visits	Group (Ref=Fixed-only)	Accel	1.45	-0.69,3.59	0.18	1.01	-0.89,2.90	0.29
		Sham	-0.97	-3.20,1.25	0.39	-0.11	-2.10,1.88	0.91
	Gender		NT			0.10	-0.92,1.13	0.84
	Irregularity T1		NT			-0.13	-0.40,0.14	0.33
	PAR T1		NT			0.05	-0.03,0.12	0.20
	Center (Ref=Brighton)	Guys	NT			4.24	1.81,6.67	0.001
		Ashford	NT			2.81	0.97,4.64	0.003
Number of breakages	Group (Ref=Fixed-only)	Accel	0.16	-1.10,1.42	0.80	0.10	-1.12,1.32	0.87
		Sham	-0.09	-1.40,1.21	0.89	-0.31	-1.60,0.97	0.63
	Malocclusion		NT			0.63	-0.03,1.29	0.06
	PAR T1		NT			-0.01	-0.06,0.04	0.68
	Center (Ref=Brighton)	Guys	NT			-0.85	-2.36,0.66	0.26
		Ashford	NT			1.04	-0.15,2.23	0.09
Change in PAR	Group (Ref=Fixed-only)	Accel	-0.51	-7.43,6.42	0.88	-0.35	-1.60,0.90	0.57
		Sham	-2.37	-9.46,4.72	0.51	0.69	-0.62,2.01	0.30
	PAR T1		NT			0.98	0.93,1.03	<0.001
	Center (Ref=Brighton)	Guys	NT			0.86	-0.67,2.39	0.26
		Ashford	NT			-1.37	-2.54,-0.19	0.02
% change in PAR	Group (Ref=Fixed-only)	Accel	-2.22	-6.52,2.08	0.31	-1.54	-5.10,2.03	0.39
		Sham	1.19	-3.22,5.59	0.59	2.78	-0.98,6.54	0.14
	PAR T1		NT			0.31	0.17,0.45	<0.001
	Center (Ref=Brighton)	Guys	NT			3.21	-1.15,7.57	0.15
		Ashford	NT			-4.31	-7.67,-0.96	0.01

b, unstandardized coefficient; CI, confidence interval; NT, not tested; Ref, reference; PAR, peer assessment rating.

SUPPLEMENTARY DATA

Supplementary Table 1. Explorative assessment of mean time intervals between appointments.

	Accel-group			Sham-group			Fixed-only group			
	n	median	IQR	n	median	IQR	n	median	IQR	P*
Time interval in days	22	50.7	45.7, 55.4	19	52.3	46.0, 57.4	20	48.3	44.7, 55.1	0.297

IQR, interquartile range
* from Kruskal-Wallis test

Supplementary Table 2. Explorative assessment for interaction effects on primary and secondary outcomes of severe irregularity at baseline, severe spaces at T1, and severe PAR at baseline. Significant P values indicate that the effect of randomized intervention on listed outcome differs between patients with severe and non-severe conditions.

	P value for interaction		
	Severe irregularity (>7mm)	Severe spacing (>7mm)	Severe PAR (>30 points)
Initial rate of space closure (T1-T2)	0.708	0.756	0.399
Treatment duration (months)	0.235	0.347	0.785
% change in PAR	0.958	0.239	0.056

PAR, peer assessment rating.

Supplementary Table 3. Results of reliability and agreement of repeated measurements

	Mean	95% Limits of agreement	P (correlation: difference-mean)
Limits of agreement	-0.027	-1.044, 0.991	0.622
	CCC	95% CI	P
CCC	0.999	0.999, 1.000	<0.001

CCC, Concordance correlation coefficient; CI, Confidence Interval.

Supplementary Table 4. Demographics of the trial subjects (Intention-to-Treat analysis)*

Characteristic	Overall	Accel	Sham	Fixed-only
Patient number - n	64	24	19	21
Center (Brighton) - n (%)	27 (42%)	8 (33%)	11 (58%)	8 (38%)
Center (Guy's) - n (%)	11 (17%)	4 (17%)	1 (5%)	6 (29%)
Center 3 – (Canterbury) (%)	26 (41%)	12 (50%)	7 (37%)	7 (33%)
Male - n (%)	31 (48%)	11 (46%)	8 (42%)	12 (57%)
Age - mean (SD)	14.0 (1.8)	13.8 (1.8)	13.9 (1.5)	14.5 (2.0)
Baseline irregularity - mean (SD)	7.9 (3.3)	7.8 (3.6)	7.9 (3.3)	8.0 (3.2)
Baseline PAR - mean (SD)	32.8 (10.9)	33.5 (11.3)	30.9 (9.6)	33.9 (11.9)
Class I - n (%)	24 (38%)	9 (38%)	7 (37%)	8 (38%)
Class II - n (%)	22 (34%)	9 (38%)	6 (32%)	7 (33%)
Class III - n (%)	18 (28%)	6 (25%)	6 (32%)	6 (29%)
Premolar extractions - n (%)	56 (88%)	23 (96%)	17 (89%)	16 (76%)
Canine/incisor extractions - n (%)	2 (3%)	0 (0%)	0 (0%)	2 (10%)
Mixed extractions - n (%)	6 (9%)	1 (4%)	2 (11%)	3 (14%)

SD, standard deviation; PAR, peer assessment rating
*n=61, not 64 patients (23, 19 and 19 subjects in Accel, Sham, and Fixed-only groups, respectively)

Supplementary Table 5. Descriptive statistics and crude differences across groups. Data are given as medians and IQR and not as means and SDs, as they are not normally distributed (Intention-to-Treat analysis)

	Accel-group			Sham-group			Fixed-only group			
	n	median	IQR	n	median	IQR	n	median	IQR	P*
Initial rate of space closure rate (T1-T2) (mm/month)	24	0.74	0.45,1.24	19	0.89	0.56,1.13	21	0.94	0.62,1.44	0.592
Overall rate of space closure (T1-T3) (mm/month)	23	0.80	0.62,1.06	19	0.68	0.57,0.80	19	0.76	0.52,1.01	0.442
Treatment duration (months)	24	20.45	18.05,25.92	19	16.73	15.33,22.07	20	17.64	14.87,23.89	**0.046**
No of visits	24	14.5	11.5,16.5	19	11.0	10.0,14.0	20	11.0	9.5,16.0	0.108
No of breakages	24	2.0	1.0,4.0	19	2.0	1.0,3.0	20	2.0	1.0,2.0	0.803
PAR at T4	23	3.0	2.0,6.0	19	3.0	2.0,4.0	19	3.0	2.0,4.0	0.628
PAR Improvement	23	26.0	21.0,38.0	19	27.0	20.0,35.0	19	29.0	24.0,31.0	0.897
PAR Improvement %	23	88.9	80.9,94.4	19	90.0	87.5,92.0	19	91.2	85.0,93.5	0.749

PAR, peer assessment rating
* from Kruskal-Wallis test

Supplementary Table 6. Results of crude and adjusted regression models for primary and secondary outcomes (Intention-to-Treat analysis)

			Crude model: only group and center effects				Adjusted modeling: group, center, and confounding		
			b	95% CI	P		b	95% CI	P
Monthly space closure rate T1-T2	Group (Ref=Fixed-only)	Accel	-0.09	-0.42,0.23	0.569		-0.10	-0.40,0.21	0.529
		Sham	0.01	-0.33,0.35	0.964		-0.00	-0.31,0.31	0.994
	Gender		NT				0.33	0.08,0.59	0.011
	Malocclusion		NT				0.08	-0.07,0.24	0.304
	Extraction		NT				0.26	0.05,0.48	0.016
	PAR T1		NT				-0.00	-0.01,0.01	0.988
	Spaces T3		NT				0.07	0.01,0.12	0.013
Monthly space closure rate T1-T3	Group (Ref=Fixed-only)	Accel	0.07	-0.19,0.33	0.607		0.13	-0.12,0.38	0.317
		Sham	-0.13	-0.40,0.14	0.351		-0.10	-0.36,0.16	0.450
	Gender		NT				0.19	-0.03,0.40	0.087
	Malocclusion		NT				0.12	-0.01,0.25	0.082
	Extraction		NT				0.13	-0.05,0.30	0.157
	PAR T1		NT				0.01	-0.00,0.02	0.075
	Spaces T3		NT				0.06	0.01,0.10	0.012
Treatment duration in months	Group (Ref=Fixed-only)	Accel	3.09	0.16,6.02	0.039		2.57	-0.26,5.40	0.076
		Sham	0.52	-2.62,3.66	0.747		0.61	-2.42,3.64	0.694
	Gender		NT				-1.11	-3.46,1.24	0.355
	PAR T1		NT				0.11	-0.01,0.22	0.063
Number of visits	Group (Ref=Fixed-only)	Accel	1.34	-0.42,3.09	0.136		1.03	-0.69,2.75	0.240
		Sham	-0.27	-2.15,1.62	0.782		-0.16	-2.00,1.68	0.864
	Gender		NT				0.07	-1.36,1.50	0.923
	PAR T1		NT				0.06	-0.01,0.12	0.099
Number of breakages	Group (Ref=Fixed-only)	Accel	0.10	-1.00,1.20	0.858		0.15	-1.00,1.29	0.801
		Sham	-0.17	-1.35,1.01	0.783		-0.19	-1.41,1.03	0.761
	Gender		NT				-0.20	-1.15,0.76	0.688
	PAR T1		NT				-0.00	-0.05,0.04	0.913
Change in PAR	Group (Ref=Fixed-only)	Accel	-0.88	-7.25,5.49	0.786		-0.31	-1.47,0.85	0.601
		Sham	-2.37	-9.04,4.30	0.486		0.54	-0.70,1.78	0.395
	Gender		NT				-0.45	-1.41,0.51	0.360
	PAR T1		NT				0.97	0.92,1.01	<0.001
% change in PAR	Group (Ref=Fixed-only)	Accel	-1.61	-5.51,2.29	0.420		-1.23	-4.57,2.12	0.472
		Sham	1.50	-2.62,5.62	0.475		2.27	-1.31,5.84	0.214
	Gender		NT				-1.85	-4.63,0.93	0.192
	PAR T1		NT				0.28	0.14,0.41	<0.001

b, unstandardized coefficient; CI, confidence interval; NT, not tested; PAR, peer assessment rating.

Supplementary Table 7. Explorative assessment of mean time intervals between appointments (Intention-to-Treat analysis)

	Group 1				Group 2				Group 3			
	n	median	IQR		n	median	IQR		n	median	IQR	P*
Time interval in days	24	50.7	47.8,55.4		19	52.3	46.0,57.4		20	48.3	44.7,55.1	0.279

IQR, interquartile range
* from Kruskal-Wallis test

Supplementary Table 8. Explorative assessment for interaction effects on the primary/secondary outcomes of severe irregularity at baseline, severe spaces at T1, and severe PAR at baseline. Significant p values indicate that the effect of randomized intervention on the listed outcome differs between patients with severe and non-severe conditions (Intention-to-Treat analysis).

	P value for interaction		
	Severe irregularity (>7mm)	Severe spacing (>7mm)	Severe PAR (>30 points)
Monthly space closure rate T1-T2	0.484	0.563	0.433
Treatment duration in months	0.112	0.121	0.969
% change in PAR	0.852	0.343	0.139

PAR, peer assessment rating.